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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/934,113	HODGSON, CLAGUE P.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-90* is/are pending in the application.

4a) Of the above claim(s) *86 and 87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-85 and 88-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 10-25-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 88-90 have been added. Claims 77-90 are pending and under consideration in the instant office action.

Election/Restrictions

Applicant's election without traverse of Group I, claims 77-85, in the response filed 9-22-03 is acknowledged.

This application contains claims 86 and 87 drawn to an invention nonelected with traverse in the paper filed 9-22-03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 77-85 and 88-90 are under consideration in the instant office action.

Priority

The status of 08/622,336 has been updated to reflect that 08/622,336 is now US Patent 6,287,863.

The status of 08/030766, now abandoned, has been updated in the first line of the specification.

Specification

The descriptions of Fig. 4 and 5 on pg 13, line 27, has been separated in different paragraphs.

The descriptions of Fig. 7 and 8 on pg 14, line 2, has been separated in different paragraphs.

The description of Fig. 7 has been amended to begin Fig. 7A-7D.

The description of Fig. 8 has been amended to begin Fig. 8A-8D.

The status of the application on pg 3, line 27, and pg 43, line 29, has been updated.

Claim Objections

The term "which" throughout the claims has been replaced with --that-- as requested by the examiner.

The last step of claims 77 and 80 should more clearly set forth that the DNA is expressed in the animal. The phrase --so that the DNA sequence is expressed in the animal-- would overcome this rejection.

Claim Rejections - 35 USC § 112

Claims 77-85 remain rejected and claims 88-90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The rejection regarding "from step (d)(1)" (77, 80-82, 84, 85) has been withdrawn because the phrase has been deleted.

The rejection regarding the phrase "identifying a transformed cell which contains the DNA sequence of (a)(vi)" (77, 80, 85) has been withdrawn in view of the amendment to the claims.

The rejection regarding the phrase "wherein the cell is an embryonic stem cell..." in claim 78 as new matter has been withdrawn in view of pg 51, lines 16 and 32.

The rejection regarding the phrase "capable of packaging nucleic acid molecules into a virion to yield a transformed donor cell" (80) has been withdrawn because the phrase has been deleted.

The rejection regarding the phrase "producing a double-stranded cDNA containing a gene which is capable of homologous recombination with the genome of a cell" (81) has been withdrawn because the phrase has been deleted.

The rejection regarding the phrase "inserted into the vector 3' of the transcription initiation site... ...with the genome of the cell" (81) has been withdrawn in part because part of the phrase has been deleted.

The rejection regarding the phrase "identifying a cell which contains an integrated form of the vector... ...which is capable of homologous recombination with the genome of the cell" (81) has been withdrawn because the phrase has been deleted.

The rejection regarding the phrase "reconstituting tissues with genetically modified embryonic stem cells" (82) has been withdrawn because the phrase has been amended.

The rejection regarding the phrase "preparing genetically modified ES cells" (84) has been withdrawn because the phrase has support on pg 51, line 16.

The claims remain rejected under new matter for reasons of record as follows:

The phrase "expressing a DNA sequence in an animal" (77, 80) remains new matter. Applicants argue pg 10, line 8, page 11, line 21 through page 12, line 9, page 37, lines 7, 12-13, 30, and 32, page 47, lines 18-30, page 50, lines 26-27, page 53, lines 16-22, page 55, line 26 through page 56, line 4, and Figure 13C, provide support for the phrase. The citations have been reviewed and applicants' arguments are not persuasive. For example, pg 10, line 8, states "capture the promoter is adapted as a gene therapy vector also, since during retrotransposon transmission, the promoter (U3) region of the LTR at the 3'-end of the vector is also copied to the 5'-end, making both LTRS uniform." Pg 10, line 8, does not describe expressing the DNA in an animal as claimed. None of the other citations suggest expressing the DNA sequence in an animal as claimed. Please point to one citation where the specification contemplates or provides an example of expressing the DNA sequence in an animal.

The phrase "introducing the transformed cell to an organ of an animal, tissue of an animal, an embryo of an animal or an animal" (77, 80, 82) remains new matter. Applicants argue pg 10, line 8, page 11, line 21 through page 12, line 9, page 37, lines 7, 12-13, 30, and 32, page 47, lines 18-30, page 50, lines 26-27, page 53, lines 16-22, page 55, line 26 through page 56, line 4, and Figure 13C, provide support for the phrase. The citations have been reviewed and applicants' arguments are not persuasive. For example, pg 10, line 8, states "capture the promoter is adapted as a

gene therapy vector also, since during retrotransposon transmission, the promoter (U3) region of the LTR at the 3'-end of the vector is also copied to the 5'-end, making both LTRS uniform." Pg 10, line 8, does not describe delivering transformed cells to an organ, tissue, embryo or animal as claimed. Pg 47, lines 18-30, suggests rescuing stem cells from the bone marrow or peripheral blood and reintroducing genetically engineered blood stem cells (BSC) into the blood. Pg 47, lines 18-30, do not suggest introducing any transformed cell into any organ, tissue, embryo or animal as broadly claimed. Pg 51, lines 16-33, specifically, pg 51, lines 16 and 32, suggest modifying ES cells with a vector encoding histocompatibility antigens or to "deliver therapeutic genes to bone marrow transplantation recipients." Pg 51 is limited to ES cells delivered to the blood and does not encompass delivering any cell to any organ, tissue, embryo or animal as broadly claimed. pg 53, lines 16-22, suggest transfecting ES cells with the vector to make transgenic animals. Pg 53 is limited to introducing transformed ES cells into embryos. Pg 55, line 26, through pg 56, line 4, is also limited to introducing transformed ES cells into embryos. Fig. 13C does not describe the vector was introduced in the context of a transformed cell into the chicken *in vivo* (pg 14, lines 16-19). Please point to one citation where the specification contemplates or provides an example of introducing a transformed cell into an organ, tissue or animal. Please point to a citation where the specification contemplates introducing transformed cells other than bone marrow stem cells or ES cells into an animal. Please point to a citation where the specification contemplates introducing transformed cells into a tissue or organ of an animal.

The phrase "wherein the cell is... ... a pluripotent stem cell" in claim 78 remains rejected under new matter for reasons of record. Pg 47, lines 18-30, suggests rescuing stem cells from the bone marrow or peripheral blood and reintroducing genetically engineered blood stem cells (BSC) into the blood. Pg 47, lines 18-30, is limited to bone marrow stem cells and does not suggest using any pluripotent stem cell as broadly claimed.

The phrase "a polyd(T) tract 3' to an open reading frame" in claim 81 remains new matter. Applicants point to pg 35, line 5, through pg 36, line 20 and Figure 9. Applicants' argument is not persuasive. The citations do not teach the DNA in the 5' LTR had a "polyd(T) tract 3' to an ORF as claimed.

The phrase "where the embryonic stem cell has been modified with respect to the histocompatibility antigens present on the stem cell surface" (83) remains new matter for reasons of record. Applicants argue the phrase is found on pg 51, lines 22-31. Applicants' argument is not persuasive. Pg 51, lines 16 and 32, suggest modifying ES cells with a vector encoding histocompatibility antigens or to "deliver therapeutic genes to bone marrow transplantation recipients." Pg 51 is limited to genetically modifying ES cells to deliver new histocompatibility antigens. Pg 51 does not use the phrase "with respect to the histocompatibility antigens" or contemplate the scope of "histocompatibility antigens on the stem cell surface" as claimed.

The phrase "autonomously replicating DNA sequences to the genome of a recipient cell" (85) remains new matter. Applicants argue the phrase has support on pg 59, line 29, through pg 61, line 30, and Fig. 14. Applicants' argument is not persuasive.

The citation describes autoexcision of episomal vector and "autonomous existence" but does not suggest the DNA sequence replicates autosomally. Clarification is required.

Claims 77-85 remain rejected and claims 88-90 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for introducing a vector into a packaging cell *in vitro,* wherein said vector comprises (i)-(v) and (vii) of claim 77, step a) (without the phrase ("from step (d)(1)") and a nucleic acid sequence encoding a protein, introducing a viral particle made by the packaging cell into a cell *in vitro*, and expressing the protein in the cell, does not reasonably provide enablement for using the method to make transgenic animals other than mice and chickens, for using the method in gene therapy or for using the method to transduce any ES cell other than mouse ES cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claims 78, 82, 83 and 84 specifically require transforming embryonic stem cells and introducing the ES cells into an animal. Claims 77, 78 and 80-85 require introducing a donor cell into an embryo and detecting the vector in an organ, tissue, embryo or animal. The only purpose for introducing transformed cells into an embryo or for introducing transformed ES cells into an tissue, organ or animal is to make transgenics. Therefore, claims 77, 78 and 80-85 are being examined as they relate to making transgenics.

ES cells are defined as being totipotent, i.e. be capable of germline transmission upon being introduced into a recipient embryo (see definition of ES cells by New Dictionary of Cultural Literacy provided).

Applicants' arguments regarding Vick and chicken PGC capable of contributing to the germline upon being introduced into a recipient embryo are persuasive.

Thus, the state of the art at the time of filing was that ES cells capable of germline transmission in species other than mice and chickens did not exist. In chickens, stage XI PGCs had been isolated from chickens, transduced with retrovirus, and immediately injected into the vasculature of Stage 15 chick embryos to obtain germline transmission of a transgene (Vick et al., Proc. R. Soc. Lond., 1993, Vol. 251, pg 179-182; pg 181, col. 1, 1st partial ¶). The PGCs described by Vick are effectively ES cells because they are capable of germline transmission upon being introduced into recipient embryos. While embryonic cells had been isolated in other species, the cells did not proliferate in culture and were not capable of making germ cells upon being introduced into an embryo (Bradley, 1992, Biotechnology, Vol. 10, pg 534-539; sentence bridging pg 537-538; Seamark, 1994, Reproductive Fertility and Devel., Vol. 6, pg 653-657; pg 6, abstract).

Since the effective filing date of applicants invention, Mullins (1996, J. Clin. Invest., Vol. 98, pg 1557-1560) taught that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated" (pg 1158, col. 2, lines 6-10). The specification suggests using the vector to transform cells

injected into embryos for the purpose of making transgenics of any species (pg 53, lines 16-22). The specification does not teach how to obtain ES cells in any species. Without such guidance taken with the state of the art, it would have required one of skill undue experimentation to work with ES cells as claimed in any species other than mice and chickens. Therefore, the claims should be limited to using mouse or chicken ES cells.

Applicants argue 5,843,780 enabled one of skill to obtain ES cells in species other than mice. Applicants' argument is not persuasive. '780 was not available at the time of filing. In fact, '780 was not filed until after the effective filing date of the instant application (3-14-94). Therefore, '780 cannot be relied upon for what was known at the time of filing.

Applicants argue Evans, Notananni, Giler, Graves, Sukoyan, Sukoyan and Iannaccone enable one of skill to obtain pluripotent cells from embryos of several domestic and laboratory animals. Applicants' arguments are not persuasive. The only ES cells described in Evans, Notananni, Giler, Graves, Sukoyan, Sukoyan and Iannaccone are mouse ES cells. Pluripotent cells from embryos in other species are not ES cells as claimed because they are not capable of germline transmission upon being implanted into a recipient embryo – a requirement for ES cells as defined in the art at the time of filing.

Applicants argue Seamark taught "pluripotent ES cells can be created for the majority of livestock breed". Applicants' argument is not persuasive. Seamark specifically goes on to say the cells are not passed on through the germline. Therefore,

the "ES cells" described by Seamark are not totipotent because they are not capable of germline transmission upon being transplanted into a recipient embryo.

Applicants' arguments regarding Mullins and Wall are not persuasive because Mullins and Wall did not teach how to obtain ES cells capable of germline transmission in species other than mice and chickens.

Applicants' arguments regarding Grunkemeyer (2001) are not persuasive because the reference was not available at the time of filing. Therefore, Grunkemeyer cannot be relied upon to establish what was known at the time of filing.

Applicants' arguments regarding Staplin (2002) are not persuasive because the reference was not available at the time of filing. Therefore, Staplin cannot be relied upon to establish what was known at the time of filing.

Applicants' argument regarding Hammer (1990) is not persuasive because Hammer did not introduce transformed ES cells comprising a vector encoding histocompatibility antigens into an organ tissue, embryo or animal as claimed.

Applicants' argument regarding Wright (1991) is not persuasive because Wright has not been provided and cannot be considered. It is not readily apparent that Wright transformed sheep ES cells with a vector encoding human α 1-antitrypsin and introduced the transformed ES cells into a tissue, organ or embryo as claimed to make the transgenic sheep.

Applicants' argument regarding Ebert (1991) is not persuasive because Ebert has not been provided and cannot be considered. Ebert did not transform goat ES cells

with a vector encoding plasminogen activator and introduce the transformed ES cells into a tissue, organ or embryo as claimed to make the transgenic goat.

Claims 77-85 require introducing a vector or cell comprising a vector into an "organ of an animal, tissue of animal... ...or an animal". The only purpose disclosed for such a method is for treatment, i.e. gene therapy. Claim 82 specifically is directed towards "introducing genetically modified ES cells." However, the specification does not enable one of skill to introduce a retroviral vector or cell comprising a retroviral vector into an animal such that a therapeutic effect occurs.

While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pg 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (pg 198, col. 1). Crystal (1995, Science, Vol. 270, pg 404-410) also reviews various vectors known in the art and indicates, "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (pg 409). Therefore, the state of the art was that the parameters required to obtain a therapeutic effect were unpredictable.

Since the time of filing, the art of gene therapy continued to be unpredictable. Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69) taught that the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" prevented obtaining a therapeutic effect using gene therapy (pg 53, 1st ¶). Verma (Sept. 1997, Nature, Vol. 389, pg 239-242) reviewed retroviral vectors known in the art for use in gene therapy and discussed problems associated with them. Verma taught that in 1997, vector targeting to the tissue required to obtain the desired effect had not yet been achieved (see entire article).

The specification merely provides generic teachings and statements regarding gene therapy and treatment using a retrovirus. For example the paragraph bridging pg 47-48 discusses reconstituting an animal with hematopoietic stem cells expressing growth factors to treat disease. However, the specification does not teach the growth factor or amount of growth factor required to treat any disease or how to obtain adequate expression of a growth factor in vivo using the vector of the invention so that therapeutic levels of expression occur in the desired tissue. The specification does not teach the specific combination of elements required to overcome the unpredictabililty in the art by teaching the specific combination of elements required to obtain a therapeutic effect using a retrovirus as claimed. I.e. the specification does not teach the specific combination of promoter, protein, tissue of interest, amount of expression and route of administration required to introduce a retrovirus into a tissue or organ of animal or anywhere into an animal as claimed such that a therapeutic effect would occur. Based on the unpredictability in the art taken with the dearth of information in the specification,

it would require one of skill undue experimentation to determine the combination of elements required to obtain such an effect using a retrovirus as claimed. Therefore, the specification does not enable introducing a retrovirus or cells transduced with a retrovirus into a tissue or organ of an animal for therapy.

Applicants point to many references (Lim (1989), Flowers (1990), Garver (1987), O'Malley (1993), Rosenberg (1992), Anderson, US Patent 5,399,346), Kantoff (1987), Hatzoglou (1991), Nable (1990), Smith (1991), Price (1989), Banjerjee (1994), Vinh (1993) and Spencer (1996)) that describe obtaining expression of a gene in an animal using a retroviral vector. Applicants' arguments are not persuasive. None of the references provided taught how to use a retroviral vector to express the gene in an animal such that a therapeutic effect occurs. The lack of ability to obtain a therapeutic effect by introducing a retroviral vector into an animal is the crux of the issue, not obtaining expression.

Applicants' argument regarding Lim (1989) is not persuasive because Lim has not been provided and cannot be considered. Lim did not transform ES cells or teach obtaining a therapeutic effect.

Applicants' argument regarding Flowers (1990) is not persuasive because Flowers has not been provided and cannot be considered. Flowers did not transform ES cells or teach how to use cells expressing neo to obtain a therapeutic effect.

Applicants' argument regarding Garver (1987) is not persuasive because Garver has not been provided and cannot be considered. Garver did not transform pluripotent

cell or ES cells or teach how to use cells expressing antitrypsin to obtain a therapeutic effect.

Applicants' argument regarding O'Malley (1993) is not persuasive because O'Malley has not been provided and cannot be considered. O'Malley did not transform pluripotent or ES cells or teach how to use cells expressing a marker gene to obtain a therapeutic effect.

Applicants' argument regarding Rosenburg (JAMA, Nov. 2, 1992, Vol. 268, No. 17. pg 2416-2419) is persuasive in part. Rosenburg taught obtaining a therapeutic effect by transforming TIL with a retroviral vector encoding a marker protein and introducing the TIL back into the patient. Rosenburg did not transform pluripotent or ES cells as claimed to obtain a therapeutic effect.

Applicants' argument regarding Anderson (US Patent 5,399,346) is persuasive in part. Anderson taught obtaining a therapeutic effect by transforming T-lymphocytes with a retroviral vector encoding adenosine deaminase and introducing the T-lymphocytes back into the patient. Anderson did not transform pluripotent or ES cells as claimed to obtain the therapeutic effect.

Applicants' argument regarding Kantoff (1987) is not persuasive. Kantoff has not been provided and cannot be considered. Kantoff did not teach how to use hematopoietic stem cells expressing a marker gene or adenosine deaminase to obtain a therapeutic effect.

Applicants' argument regarding Hatzoglou (1990) is not persuasive. Hatzoglou has not been provided and cannot be considered. Hatzoglou did not transform

pluripotent or ES cells or teach how to use cells expressing a marker gene to obtain a therapeutic effect.

Applicants' argument regarding Nabel (1990) is not persuasive. Nabel has not been provided and cannot be considered. Nabel did not introduce transformed cells into the animal or teach how to obtain a therapeutic effect using the retroviral vector.

Applicants' argument regarding Banjeree (1994) is not persuasive. Banjeree was not available at the time of filing and cannot be used to establish what was known at the time of filing.

Applicants' argument regarding Vihn (1993) is not persuasive. Vihn did not introduce transformed cells into an animal or teach how to obtain a therapeutic effect using the retroviral vector.

Applicants' argument regarding Spencer (1996) is not persuasive. Spencer was not available at the time of filing and cannot be used to establish what was known at the time of filing.

Applicants' argument regarding Anderson (Science, Vol. 256, No. 5058, May 8, 1992, pg 808-813) is persuasive in part. Anderson refers to studies in which a therapeutic effect was obtained by transforming TIL with a retroviral vector encoding a marker protein and introducing the TIL back into the patient and by transforming T-lymphocytes with a retroviral vector encoding adenosine deaminase and introducing the T-lymphocytes back into the patient. Anderson did not transform pluripotent or ES cells as claimed to obtain a therapeutic effect.

Applicants' arguments regarding Miller, Crystal, Deonarain and Verma have been considered but are not persuasive. In no way do Miller, Crystal, Deonarain or Verma suggest using an ES cell or pluriopotent cell transformed with a retroviral vector was predictable. The studies cited by applicants in this regard are merely clues as to how gene therapy may be obtained. Too much further experimentation would be required given the teachings of Miller, Crystal, Deonarain and Verma taken with the teachings in the specification to obtain a therapeutic effect by transforming pluripotent cells or ES cells as claimed with a retroviral vector and introducing the cells into an animal as claimed such that a therapeutic effect would occur.

Claim 80 encompasses introducing a vector into a packaging cell and introducing the packaging cell into an embryo. The specification does not provide a use for such a method. It is assumed, therefore, that the method would be used for making transgenics and is rejected for reasons above regarding transgenics.

Claim 80 encompasses introducing a vector into a packaging cell and introducing the packaging cell into an organ of an animal, a tissue of an animal or an animal. The specification does not provide a use for such a method. It is assumed, therefore, that the method would be used for gene therapy and is rejected for reasons above regarding gene therapy.

Claim 81 requires introducing a vector to a cell using a retroviral vector with a DNA sequence "inserted into the vector 3' of the transcription initiation site in the 5' LTR of the vector which DNA sequence comprises a polyd(T) tract 3' to an open reading

frame". The specification does not teach such a method (112/1st new matter above) and cannot be found in the art. It is unclear whether such a method is used in making transgenics, gene therapy or both. Therefore, it cannot be determined how to use such a method or whether such a method is enabled. Given the absence of teachings in the specification, it would require one of skill undue experimentation to determine how to introduce a vector into a cell as claimed such that a double-stranded cDNA containing a gene capable of homologous recombination with the genome of a cell was produced.

Applicants point to Fig. 9, pg 35, line 5, through pg 36, line 20. Applicants point to Fig. 14, pg 59, line 26, through pg 61, line 30. applicant's arguments are not persuasive. The citations do not describe whether the method is used to make transgenics or for gene therapy.

Claim 85 requires "delivering an autonomously replicating DNA sequences to the genome of a recipient cell". The specification does not teach such a method (112/1st new matter above) and cannot be found in the art. The specification does not teach whether such a method is used in making transgenics, gene therapy or both. The specification does not teach what DNA sequences replicate autonomously while in the genome of a cell. Therefore, it cannot be determined how to deliver such a DNA sequence to the genome of a cell, what DNA sequences replicate autonomously or how to use such a method. Given the absence of teachings in the specification, it would require one of skill undue experimentation to determine how to deliver an autonomously replicating DNA sequence into the genome of a recipient cell as claimed.

Applicants point to Fig. 9, pg 35, line 5, through pg 36, line 20. Applicants point to Fig. 14, pg 59, line 26, through pg 61, line 30. applicant's arguments are not persuasive. The citations do not describe whether the method is used to make transgenics or for gene therapy.

Claims 77-85 remain rejected and claims 88-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The rejection of claims 77 and 80 regarding DNA sequences not being expressed "into" an animal (line 1) has been withdrawn in view of the amendment.

The rejection of claims 77, 80 and 85 because the metes and bounds of "donor cell" are unclear has been withdrawn in view of the amendment.

The rejection regarding the phrase "to yield a transformed donor cell" in step a) of claims 77, 81, 85 has been withdrawn in view of the amendment.

The rejection regarding the use of the word "linked" in step a) of claims 77, 80-82, 84, 85 has been withdrawn in view of the amendment.

The rejection regarding claim 77, 80-82, 84 and 85 because "from step (d)(1)" ((a)(iv)(2))" does not have antecedent basis has been withdrawn in view of the amendment.

The rejection regarding the phrase "introducing the transformed donor cell to" (claim 77, 80, 82, step b)) has been withdrawn in view of the amendment.

The rejection of claims 77 and 80 because step c) is not commensurate in scope with the preamble of the claim has been withdrawn in view of the amendment.

The rejection of claim 78 because an embryo is not a cell has been withdrawn in view of the amendment.

The phrase "donor cell" in claim 78 and 79 lacks antecedent basis as newly amended claim 77 no longer uses the phrase.

The rejection of claim 80 because the phrase "capable of packaging nucleic acid molecules into a virion to yield a transformed donor cell" was confusing has been withdrawn in view of the amendment.

The rejection regarding claim 81 because step b) was not commensurate in scope with the preamble of the claim has been withdrawn in view of the amendment.

The rejection regarding the phrase "which is capable of homologous recombination with the genome of the cell" (claim 81) has been withdrawn in view of the amendment.

The rejection regarding the phrase "to yield a transformed embryonic stem cell" in step a) of claims 82 and 84 has been withdrawn in view of the amendment.

The rejection regarding the term "donor cell" in claim 82, step (b) lacking antecedent basis has been withdrawn in view of the amendment.

Claims 82 and 84 remain confusing because a virion must be used to infect embryonic stem cells, but step a) i-vii) requires introducing a DNA transfer vector into an ES cell. The DNA transfer vector is introduced into a packaging cell to make a virion comprising vector RNA. Then the virion is introducing into the ES cell. At no time it the

DNA transfer vector introduced into the ES cell. Clarification is required. Applicants argue ES cells transfected with the vector can be introduced into an animal (pg 22, 2nd full ¶). Applicant's argument is not persuasive because a virion must be used to transform ES cells to introduce the vector into the cell. Introduction of a DNA vector into an ES cell would not integrate into the cell's genome or properly produce the proteins required.

The rejection of claim 82 because step c) is not commensurate in scope with the preamble of the claim has been withdrawn in view of the amendment.

The rejection of claim 82 regarding the metes and bounds of what applicants consider "reconstituted" has been withdrawn in view of the amendment.

Claim 83 remains indefinite. The metes and bounds of the structural or functional modifications that encompass "with respect to the histocompatibility antigens present on the stem cell surface" cannot be envisioned. It is unclear if the claim is limited to an ES cell in which a histocompatibility antigen has been genetically altered or if the claim encompasses an ES cell in which a protein related to histocompatibility antigen has been genetically modified, i.e. a histocompatibility antigen, an MHC molecule, or an antigen. It cannot be determined if the cell has additional proteins or is missing proteins. It is unclear if the claim is limited to an ES cell that has been genetically modified to express or to prevent expression of the protein of interest. Applicant points to pg 51, lines 22-27, however, the claim does not clearly set forth the ES cells express exogenous histocompatibility antigen as described on pg 51, lines 22-

27. Therefore, the rejection of claim 83 regarding the metes and bounds of modifications encompassed by the claim is maintained.

Claim 84 as newly amended is indefinite because the body of the claim is not commensurate in scope with the preamble of the claim. The step of introducing a vector into an ES cell as in the body of the claim is not limited to *in vitro* as in the preamble. If applicants intend the claim to be a method of preparing genetically modified ES cells *in vitro*, the body of the claim should clearly set forth that the DNA vector is introduced into the ES cells *in vitro*.

The metes and bounds of what applicants consider "autonomously replicating DNA sequences" as in the preamble and step a) (vi) of claim 85 remains indefinite for reasons of record. No such sequences can be envisioned. It is also unclear to what the sequence is "autonomous." It is unclear if the phrase is limited to a sequence that can replicate without a cell or if the phrase encompasses sequences that require a cell for replication.

Applicant argues "autonomously replicating sequences (ARS), such as transposons and mouse minute virus (Fig. 14, pg 59, line 29, through pg 61, line 30), were also known to the art prior to applicant's filing" (pg 22, last full ¶). Applicants' argument is not persuasive. While pg 59, line 29, through pg 61, line 30, discuss NVL1 and NVL2 promoters for tumor-specific or transformation specific expression, the citation does not define the metes and bounds of "autonomously replicating DNA sequences." It is not clear whether the promoters on pg 59, line 30, are autonomously replicating DNA sequences or are used to make autonomously replicating DNA

sequences. It is unclear if ARS are limited to transposons and mouse minute virus or if other ARS exist. It is unclear if any transposon or any mouse minute virus is an ARS or if only particular ones are ARS. Therefore, the rejection of claim 85 regarding the metes and bounds of "autonomously replicating DNA sequences" is maintained.

The rejection regarding the use of "recipient cell" in the preamble of claim 85 and "donor cell" in step a) of claim 85 has been withdrawn in view of the amendment.

Claim 85 remains indefinite because the body of the claim is not commensurate in scope with the preamble of the claim. The step of introducing a DNA transfer vector into a cell thereby producing a transformed cell does not result in "delivering an autonomously replicating DNA sequence to the genome of a cell" as in the preamble. If applicants intend the claim to be a method of "delivering an autonomously replicating DNA sequence to the genome of a cell", the body of the claim should clearly set forth that an autonomously replicating DNA sequence is introduced into the cell.

Double Patenting

Claims 77-85 remain rejected and claims 88-90 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,287,863. Although the conflicting claims are not identical, they are not patentably distinct from each other because they encompass using the same vector. Applicants argue claims 1-10 of '863 do not teach introducing a cell transformed as in claims 77-90, 92, 93 and 88. Applicants' argument is not persuasive. Claim 1-10 of '863 encompass introducing the recombinant virus using a

virion or a cell transformed with the virion. This is especially true upon reading claims 1-10 of '863 in view of the disclosure of '863, which is the same as the instant disclosure.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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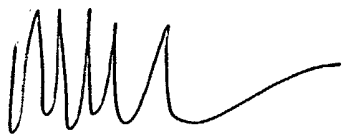
If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER